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TITLE:

# PHARMACOLOGICAL STUDY ON CENTRAL SYNAPTIC SYSTEMS AFFECTING MOTOR FUNCTION

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During the past two years, a search has been made to find an effective antagonist to Bz, a centrally acting atropine-like substance. The bioassay technique employed was the appearance of anorexia in cats shortly after administration of the drug. However, this is a time consuming procedure and does not permit a study of a large number of possible antagonist in a reasonable length of time. Therefore, an attempt has been made to develop a more rapid assay method. We have found that the effects of Bz on the EEG of conscious dogs meets these needs.

In this series of studies 100 trained dogs were used. They were rotated through the experiments every three weeks. The dogs were trained to lie quietly on lab tables. Control EEGs were obtained by inserting a needle electron beneath the scalp in the medline over the frontal regions of the cortex. The animals were then given 1.5 mgm/kgm Bz, I.V. During the first hour after injection most dogs exhibited considerable excitement. However, after this time, the animals had again quieted down and EEG recordings continued for an additional hour. At the end of that time a number of possible antagonist to Bz were injected I.V.

At the present time, the following compounds have been examined:

$R = -CH_2 - CH_2 - N(CH_3)_2HCl$

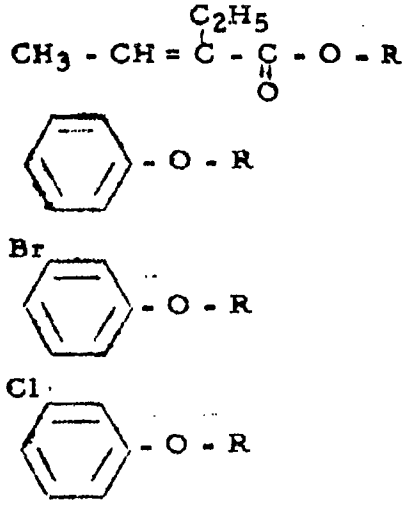
$$CH_3 = CH - \underset{\underset{O}{\|}}{C} - O - R$$

$$CH - CH = CH - \underset{\underset{O}{\|}}{C} - O - R$$

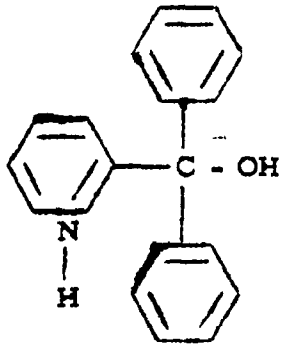
$$CH_3 - CH = \underset{\underset{O}{\|}}{\overset{\overset{CH_3}{|}}{C} - C} - O - R$$

$$CH_3 - \overset{\overset{CH_3}{|}}{C} = CH - \underset{\underset{O}{\|}}{C} - O - R$$

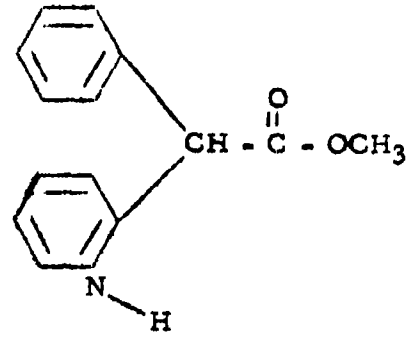
$$CH_3 - CH = \underset{\underset{O}{\|}}{\overset{\overset{C_2H_5}{|}}{C} - C} - O - R$$



All the above compounds exhibit intense nicotine-like activity. However, in doses ranging from 3 to 10 mgm/kgm, they had no effects on the electroencephalographic changes induced by Bz. Later it was found that the following two compounds were effective in reversing partially or completely the effects of Bz on the EEG:



Pipradol (Meratran)



Methylphenidate (Ritalin)

Typical EEG tracings can be found in Fig. 1 and 2. In Fig. 1, trace A is 1 hr. before, B is 1.5 hr. after 1.5 mgm/kgm Bz. Trace C is 0.5 hr. after 50 mgm Ritalin. It should be noted that there was partial to complete reversal of the EEG effects of Bz by Ritalin. After approximately 1 hr. the typical slow waves gradually returned. Recently, it has been observed that repeated injections of Ritalin at 1.5 hr. intervals will maintain the reversal for as long as 12 hr. (duration of experiments). The effects of pipradol persist for a considerably longer period of time (Fig. 2). Trace A is 1 hr. before, B is 2 hr. after 1.5 mgm/kgm Bz. Trace C 0.5 hr. after 50 mgm pipradol and D, 4 hr. later.

As pointed out above tertiary bases with nicotine-like properties

were inert in relatively large doses. During the remainder of the year we plan to investigate the effects of tertiary bases with muscarine-like actions. The following compounds will be investigated:

$$CH_3 - CH_2 - O - R$$

$$CH_3 - CH_2 - CH_2 - O - R$$

$$CH_2 = CH_2 - CH_2 - O - R$$

$$CH \equiv C - CH_2 - O - R$$

$$R = -CH_2 - CH_2 - N(CH_3)_2 \cdot HCl$$

It may be of interest to those at the Chemical Center that Bx at 1.5 mgm/kgm produces a mild hyperglycemia (see Table 1).

TABLE 1

BLOOD SUGAR MgM %

| Dog # | 8 | 9 | 10 | 11 | 13 | 7 (control) |
|---|---|---|---|---|---|---|
| Before Injection | 91 | 99 | 45 | 42 | 65 | 65 |
| 30 Min. After | 150 | 176 | 76 | 40 | 130 | 46 |
| 2 Hours After | - | - | 82 | 119 | 148 | 70 |
| 24 Hours After | 50 | 50 | 92 | 92 | 108 | - |
| 48 Hours After | 95 | 108 | - | - | - | - |

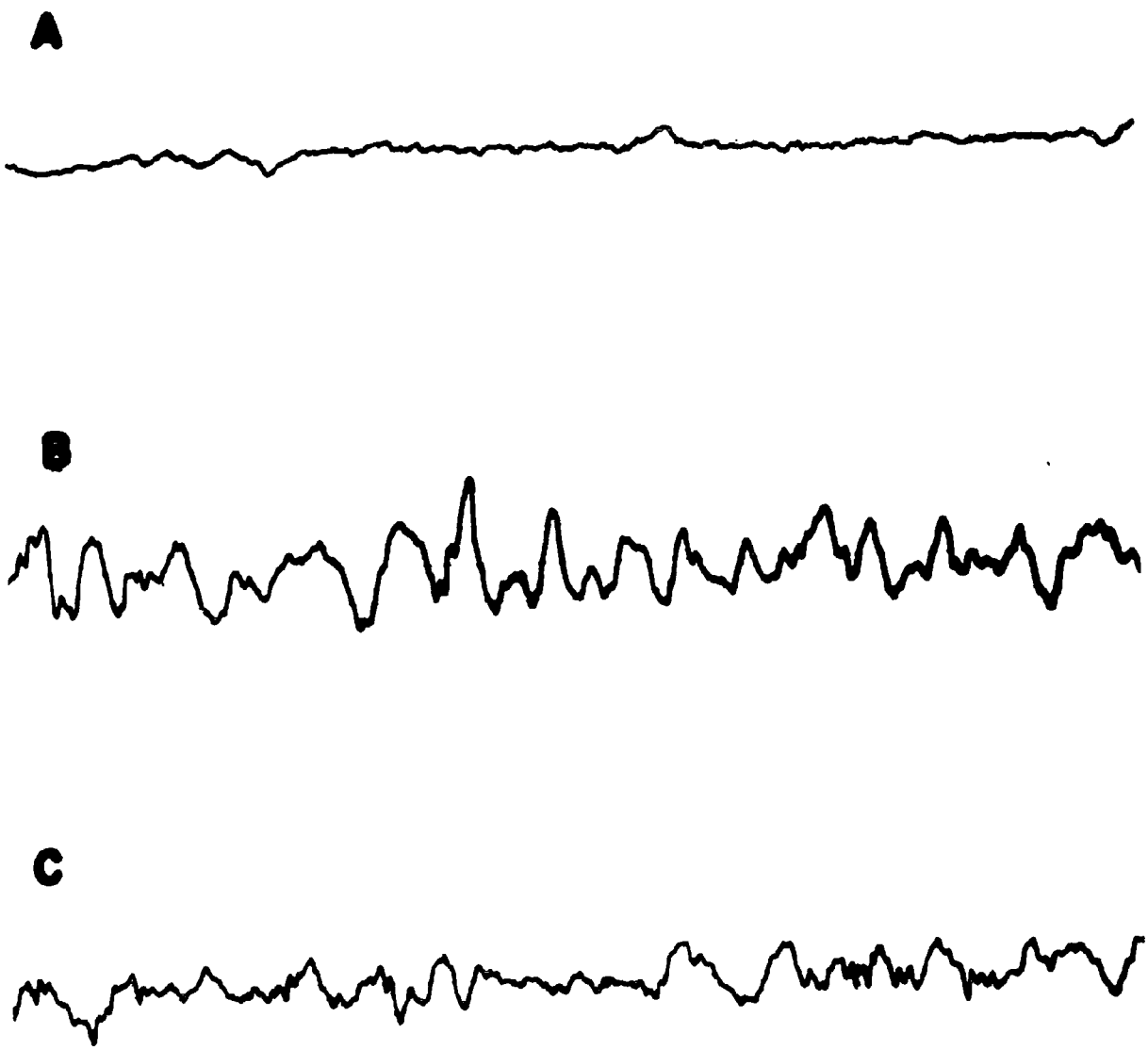



Fig. 1

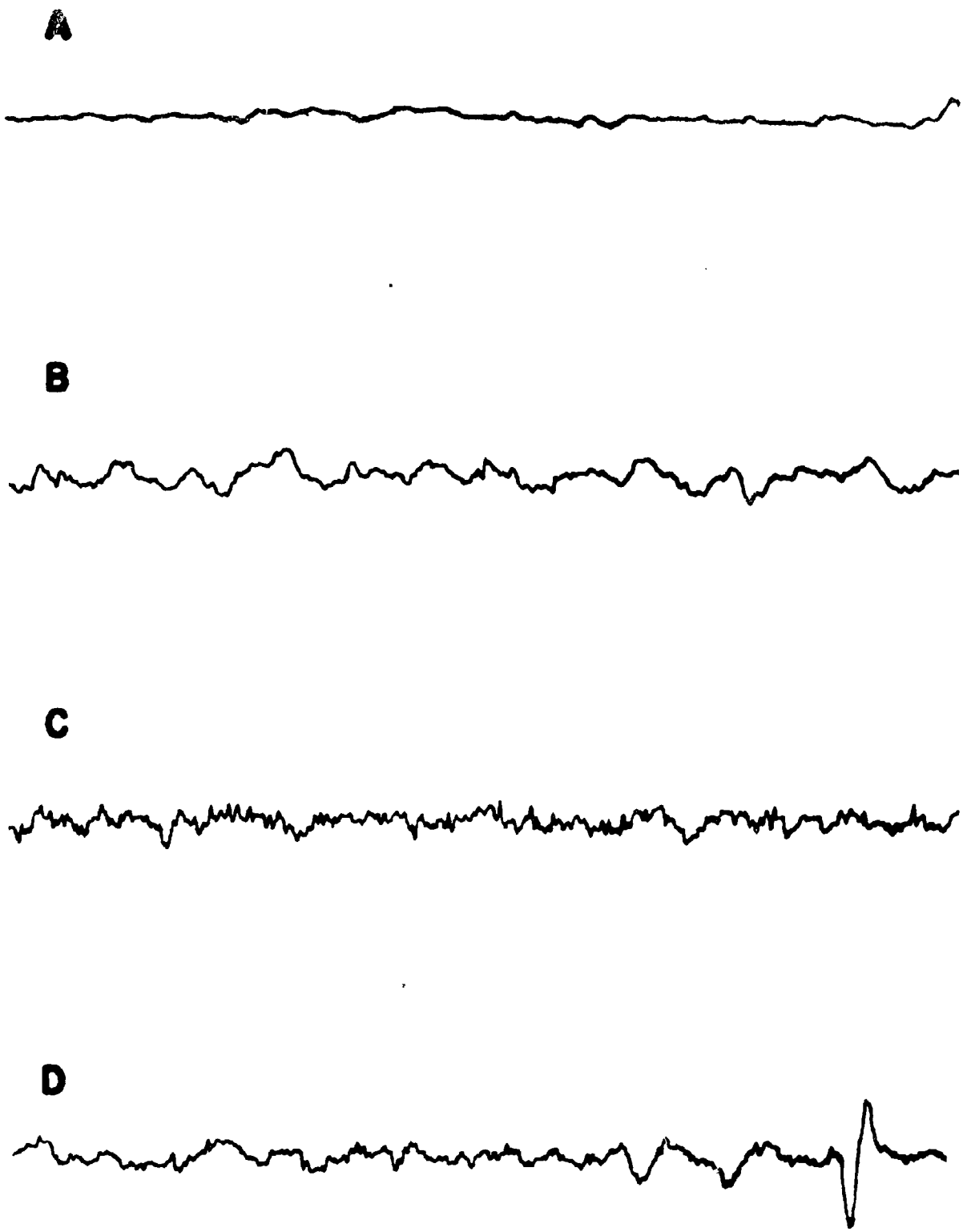



Fig. 2